



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/505, C07D 475/08</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 98/02163</b> <b>(43) International Publication Date:</b> 22 January 1998 (22.01.98)
<b>(21) International Application Number:</b> PCT/US97/11982 <b>(22) International Filing Date:</b> 16 July 1997 (16.07.97)  <b>(30) Priority Data:</b> 60/021,908 17 July 1996 (17.07.96) US  <b>(71) Applicants (for all designated States except US):</b> SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH [US/US]; 1275 York Avenue, New York, NY 10021 (US). SRI INTERNATIONAL [US/US]; 333 Ravenswood Avenue, Menlo Park, CA 94025 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> SIROTNAK, Frank, M. [US/US]; Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10021 (US). PIPER, James, R. [US/US]; Southern Research Institute, P.O. Box 55305, Birmingham, AL 35255 (US). DeGRAW, Joseph, I. [US/US]; 880 Hanover Avenue, Sunnyvale, CA 94087 (US). COLWELL, William, T. [US/US]; 1055 Del Norte, Menlo Park, CA 94025 (US).  <b>(74) Agent:</b> LARSON, Marina, T.; Oppedahl & Larson, Suite 309, 1992 Commerce Street, Yorktown Heights, NY 10598-4412 (US).		<b>(81) Designated States:</b> CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> PURIFIED COMPOSITIONS OF 10-PROPARGYL-10-DEAZAAMINOPTERIN AND METHODS OF USING SAME IN THE TREATMENT OF TUMORS		
<b>(57) Abstract</b> <p>Highly purified 10-propargyl-10-deazaaminopterin (10-propargyl-10dAM) compositions tested in xenograft models for their efficacy against human tumors are shown to be far superior to methotrexate ("MTX") and are even superior to the newer clinical candidate edatrexate ("EDX"). Moreover, 10-propargyl-10dAM showed a surprising ability to cure tumors such that there was no evidence of tumor growth several weeks after the cessation of therapy. Thus, highly purified compositions containing 10-propargyl-10dAM can be used to treat human tumors, particularly human mammary tumors and human lung cancer.</p>		

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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/11982

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/505; C07D 475/08  
US CL :514/249; 544/260

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/249; 544/260

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DEGRAW et al., Synthesis and Antitumor Activity of 10-Propargyl-10-deazaaminopterin, Journal of Medicinal Chemistry, April 1993, Vol. 36, No. 15, pages 2228-2231, especially page 2229.	1-8
Y	US 5,354,751 A (DEGRAW et al.) 11 October 1994, columns 6-7.	1-8



Further documents are listed in the continuation of Box C.



See patent family annex.

* *A* *B* *L* *O* *P*	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance earlier document published on or after the international filing date document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document referring to an oral disclosure, use, exhibition or other means document published prior to the international filing date but later than the priority date claimed	*T* *X* *Y* *A*	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art document member of the same patent family
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Date of the actual completion of the international search

26 SEPTEMBER 1997

Date of mailing of the international search report

31.10.1997

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Y	US 5,354,751 A (DEGRAW et al.) 11 October 1994, columns 6-7.	1-8



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

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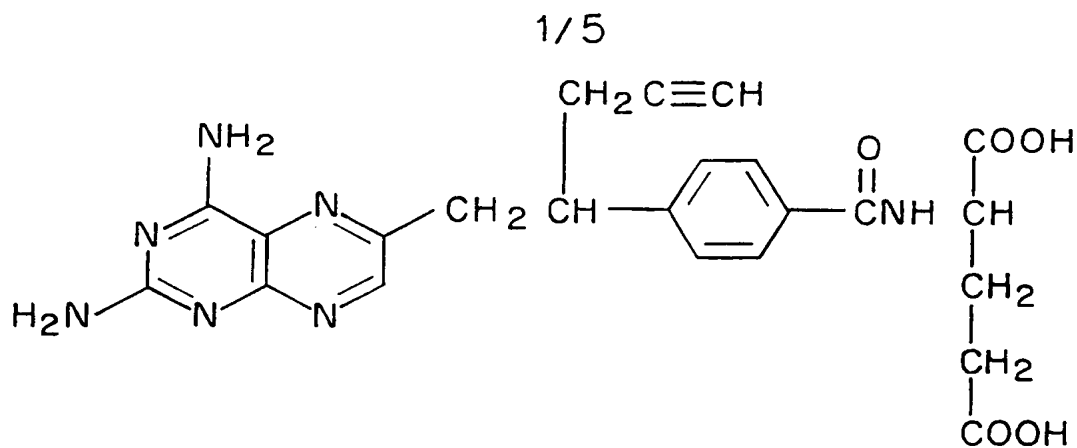


FIG. 1

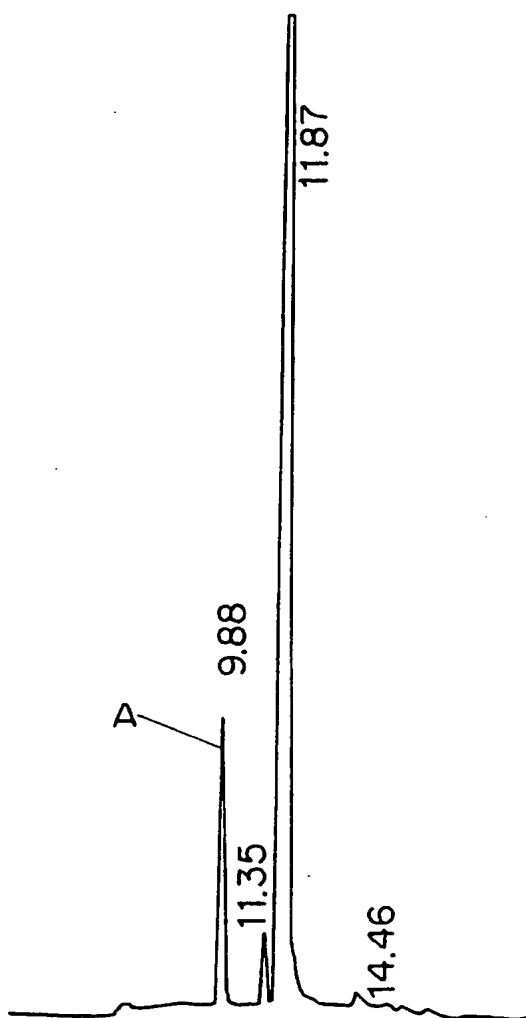


FIG. 2

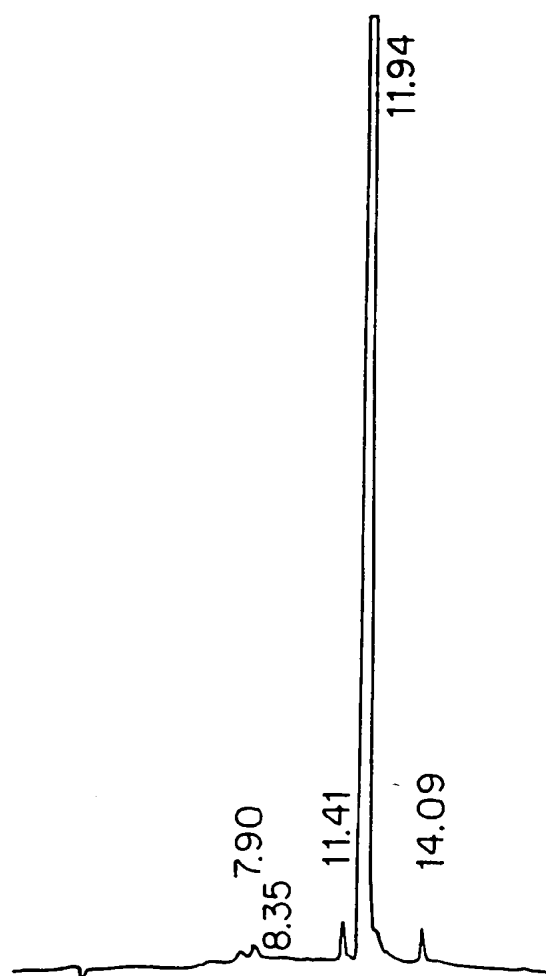
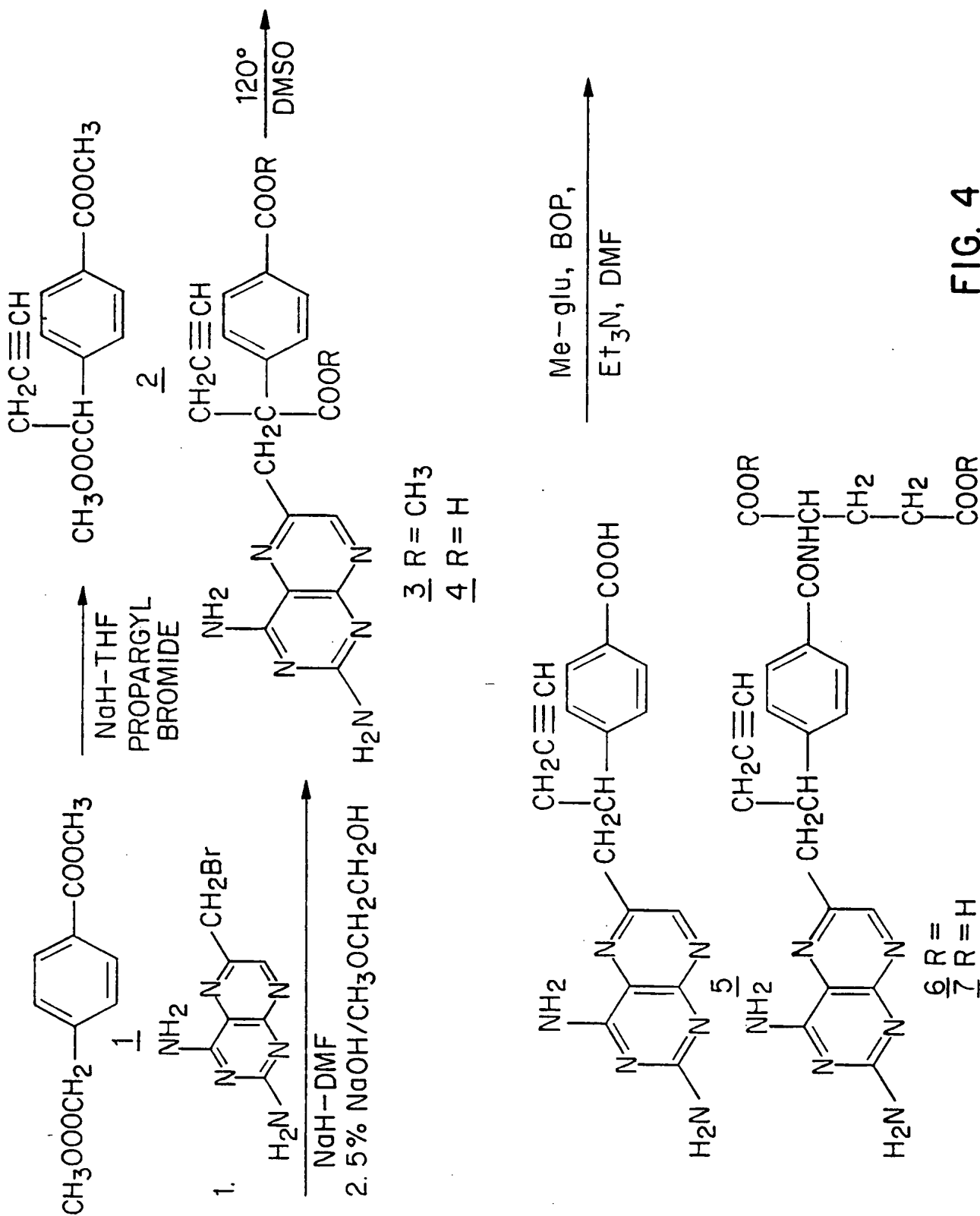


FIG. 3



**FIG. 4**

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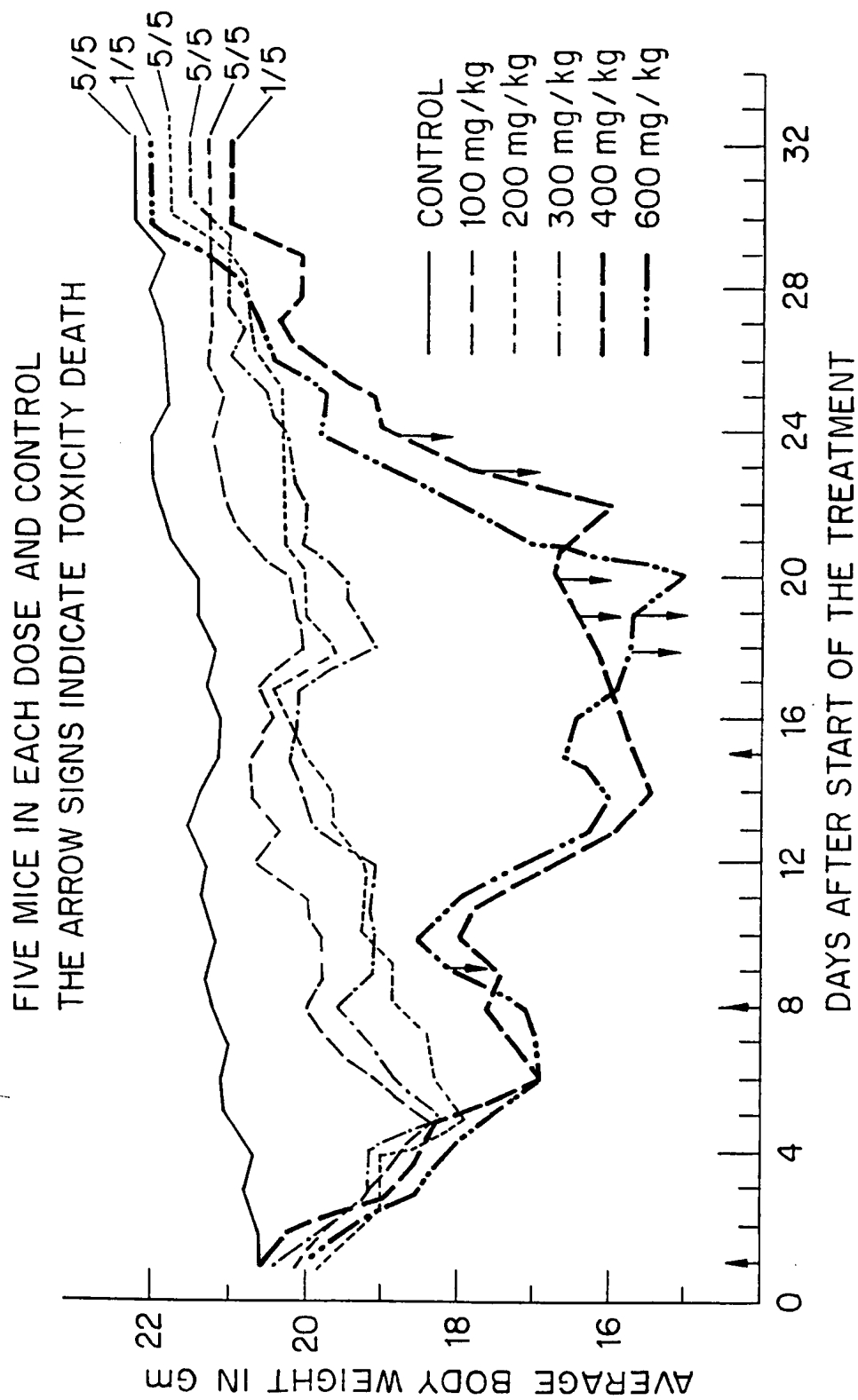


FIG. 5

4/5

FIVE RATS IN EACH DOSE AND CONTROL

THE ARROW SIGNS INDICATE TOXICITY DEATH

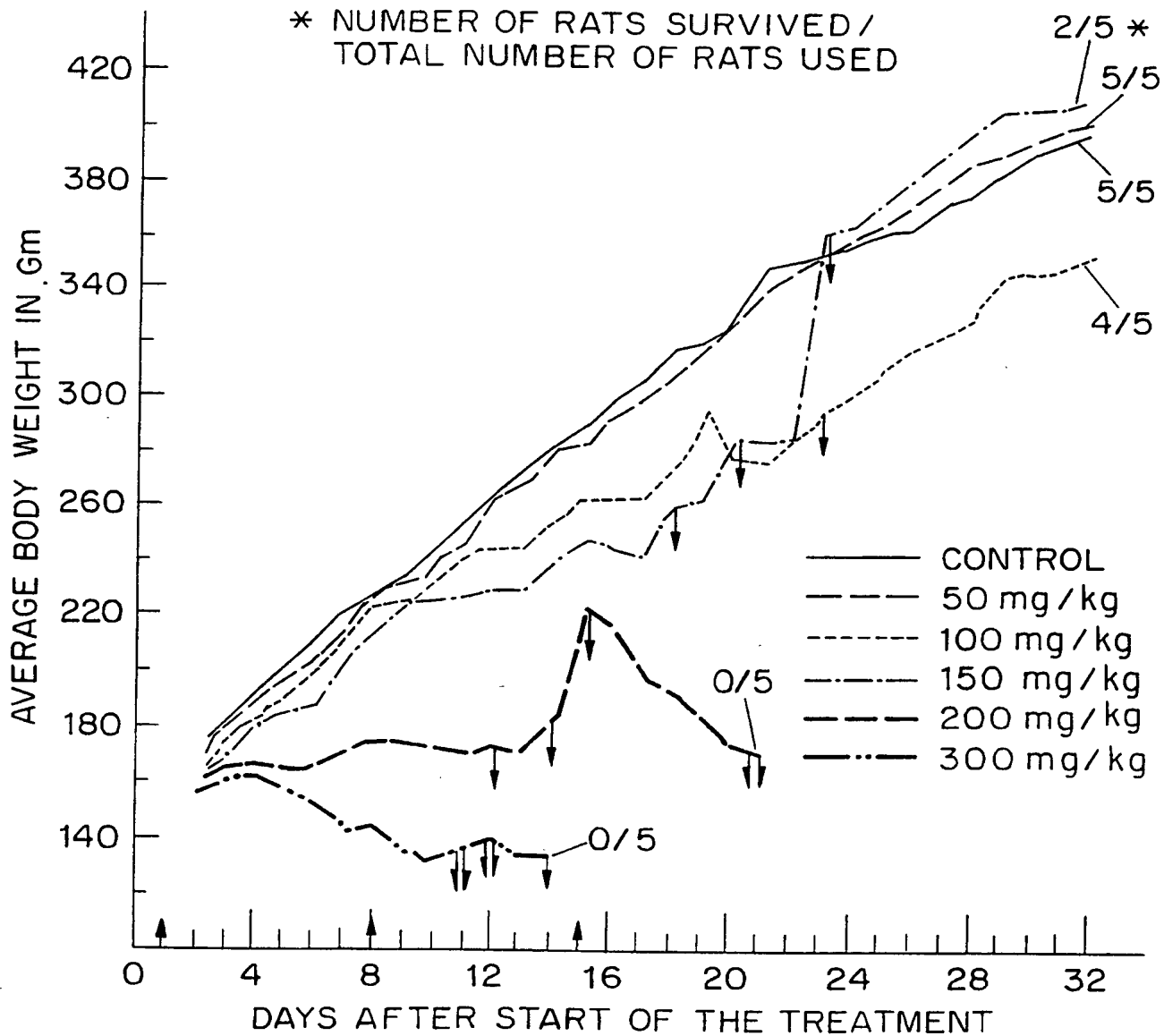
\* NUMBER OF RATS SURVIVED /  
TOTAL NUMBER OF RATS USED

FIG. 6



5/5

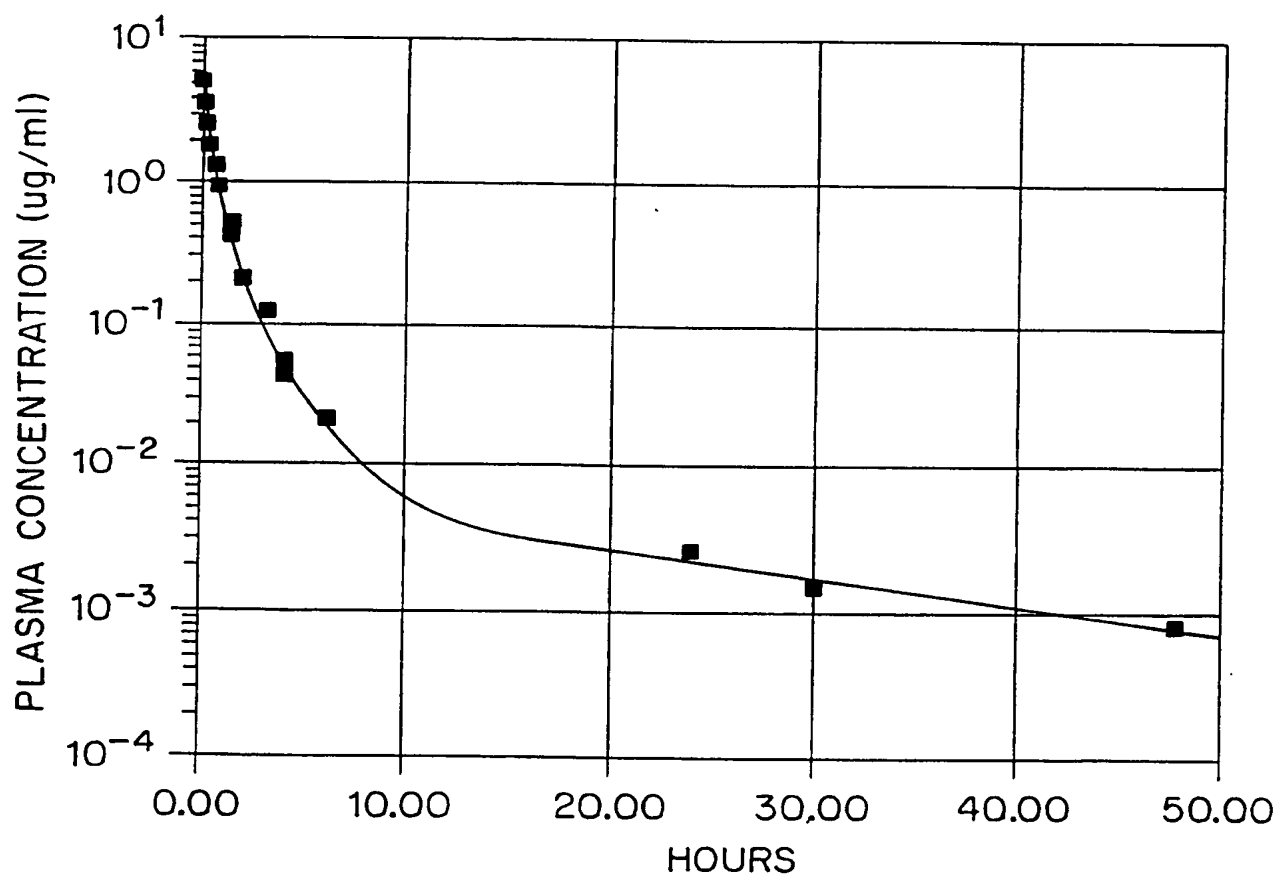


FIG. 7

## PATENT COOPERATION TREATY

PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 27 OCT 1998  
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Applicant's or agent's file reference MSKP003WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US97/11982	International filing date (day/month/year) 16 JULY 1997	Priority date (day/month/year) 17 JULY 1996
International Patent Classification (IPC) or national classification and IPC IPC(6): A61K 31/505; C07D 475/08 and US Cl.: 514/249; 544/260		
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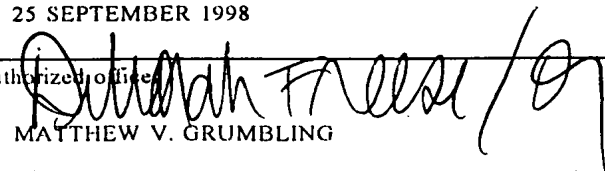
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand  10 FEBRUARY 1998	Date of completion of this report  25 SEPTEMBER 1998
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer  MATTHEW V. GRUMBLING
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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US97/11982

**I. Basis of the report**

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments):*

- ☐ the international application as originally filed.
- ☒ the description, pages (See Attached) , as originally filed.  
pages \_\_\_\_\_ , filed with the demand.  
pages \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.  
pages \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.
- ☒ the claims, Nos. (See Attached) , as originally filed.  
Nos. \_\_\_\_\_ , as amended under Article 19.  
Nos. \_\_\_\_\_ , filed with the demand.  
Nos. \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.  
Nos. \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.
- ☒ the drawings, sheets/~~fig~~ (See Attached) , as originally filed.  
sheets/~~fig~~ \_\_\_\_\_ , filed with the demand.  
sheets/~~fig~~ \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.  
sheets/~~fig~~ \_\_\_\_\_ , filed with the letter of \_\_\_\_\_.

2. The amendments have resulted in the cancellation of:

- ☒ the description, pages NONE.
- ☒ the claims, Nos. NONE.
- ☒ the drawings, sheets/~~fig~~ NONE.

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US97/11982

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. STATEMENT**

Novelty (N)	Claims	<u>1-12</u>	YES
	Claims	<u>NONE</u>	NO
Inventive Step (IS)	Claims	<u>NONE</u>	YES
	Claims	<u>1-12</u>	NO
Industrial Applicability (IA)	Claims	<u>1-12</u>	YES
	Claims	<u>NONE</u>	NO

**2. CITATIONS AND EXPLANATIONS**

Claims 1-12 lack an inventive step under PCT Article 33(3) as being obvious over Degraw et al., US 5,354,751. The reference teaches, 10-Propargyl-10-deazaaminopterin. See example 7, column 38 of the patent. This compound is taught to possess pharmaceutical activity as antifolates. The patent does not specifically teach that the 10-propargyl-10-deazaaminopterin be substantially free of deazaminotperin, nor that it be administered to mammary tumor. However, the ordinary artisan would recognize that the compounds are pharmaceuticals with antifolate activity. Antifolates are well-known as agents for the treatment of tumors as described in column 2 of the reference. Furthermore, the ordinary artisan would have been motivated to prepare pure isolates of the compounds since the ordinary artisan would have expected compounds other than the active ingredient to be potentially toxic or otherwise undesirable. There is no additional evidence on the record that would establish an unexpectedly superior result in purifying compound that was already known to possess useful pharmaceutical properties. Thus the instant claims are obvious over the Degraw et al. patent teaching.

----- NEW CITATIONS -----  
NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US97/11982

**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

**I. BASIS OF REPORT:**

This report has been drawn on the basis of the description,  
pages, 1-14, as originally filed.  
pages, NONE, filed with the demand.  
and additional amendments:  
NONE

This report has been drawn on the basis of the claims,  
numbers, 1-8, as originally filed.  
numbers, NONE, as amended under Article 19.  
numbers, 9-12, filed with the demand.  
and additional amendments:  
NONE

This report has been drawn on the basis of the drawings,  
sheets, 1-5, as originally filed.  
sheets, NONE, filed with the demand.  
and additional amendments:  
NONE